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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/541,894	12/02/2005	Karin Klokke	930008-202 (BOE0003US.NP)	6226
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EXAMINER				
SASAN, ARADHANA				
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/541,894

Applicant(s)

KLOKKERS ET AL.

Examiner

ARADHANA SASAN

Art Unit

1615

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 May 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 24-48 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 24-48 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-946)
- 3) ☐ Information Disclosure Statement(s) (PTO/SG/US)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Status of Application

1. The remarks and amendments filed on 5/5/08 are acknowledged.
2. Claims 24-48 are included in the prosecution.

Response to Arguments

Objections to the Specification

3. In light of Applicant's amendments to the Specification to appropriately denote trademarks, the objections to the Specification are withdrawn.

Rejection of claims 24-31, 34-35, 38, 40-43 and 45-48 under 35 USC § 102(b)

4. Applicant's arguments, see Pages 13-15, filed 5/5/08, with respect to the rejection of claims 24-31, 34-35, 38, 40-43 and 45-48 under 35 U.S.C. 102(b) as being anticipated by Price et al. (US 4,128,658) have been fully considered but are not persuasive.

Applicant argues that Example (c) at Col. 29 of Price et al. fails to disclose all the features of claims 24, 41 and 46 and by dependency claims 25-31, 34-35, 38, 40, 42-43, 45 and 47-48. Applicant argues that Example (c) of Price et al. does not disclose the use of any oily substance to wet the granulation mixture. Regarding the "10% solution of ... Cutina HR in Industrial Methylated Spirit OP 74" as an "oily substance", Applicant submits that such a solution of Cutina HR would not fall within the literal definition of an "oily substance". Applicant argues that the term "oily substance" does not include such solutions of Cutina HR.

This is not found persuasive because the claim limitation of an "oily substance" is anticipated by the oily substance Cutina HR, as taught by Price. Even though Cutina HR is a hydrogenated castor oil, it is still an oil or an "oily substance". The solution of Cutina HR in Example (c) of Price is clearly used to moisten or wet the mixture. This meets the limitation of wetting a mixture of active ingredients and retarding agents. A solution with an oil will, by definition, be "oily". Therefore, the solution of Cutina HR, as taught by Price, anticipates the "oily substance" limitation of instant claim 24. Price teaches that the moistened mixture in Example (c) is then granulated. This meets the granulation limitation of instant claim 24.

Therefore, the rejection of 12/5/07 is maintained.

Rejection of claims 32-33, 36-37, 39 and 44 under 35 USC § 103(a)

5. Applicant's arguments, see Pages 15-17, filed 5/5/08, with respect to the rejection of claims 32-33, 36-37, 39 and 44 under 35 U.S.C. 103(a) as being unpatentable over Price et al. (US 4,128,658) in view of Santus et al. (US 5,472,704) have been fully considered but are not persuasive.

Applicant argues that Price et al. fail to teach the use of an "oily substance" to wet a granulation mixture. Applicant argues that given the properties of Cutina HR, the claimed invention would not be achieved.

This is not persuasive because Price teaches the use of Cutina HR, which meets the claim limitation of an "oily substance". Even though Cutina HR is a hydrogenated castor oil, it is still an oil or an "oily substance".

Therefore, the rejection of 12/5/07 is maintained.

Response to Declaration by Dr. Ina Otto

6. Dr. Ina Otto submits in the Declaration (Page 2, filed 5/5/08) that the Cutina HR would precipitate on the surface of the granules as the solvent evaporates. Dr. Otto states that although this may provide a sufficient mechanism for getting additional retarding agent into the mixture, the uneven coating of the precipitated Cutina HR on the granules would have no significant effect in negating undesirable properties of the active ingredient in the particles, e.g., their hydrophilic or corrosive properties.

This is not found persuasive because even or uneven coatings are not limitations that are claimed. Dr. Otto's argument is not commensurate in scope with the claimed invention. The fact that Cutina HR will precipitate on the granules shows that there is a barrier formed on the granules. This barrier will intrinsically protect the active ingredient in the particles and will negate the undesirable properties of the active ingredient in the particles, e.g., their hydrophilic or corrosive properties.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the uneven coating of the precipitated Cutina HR on the granules) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Therefore, the rejection of 12/5/07 is maintained.

MAINTAINED REJECTIONS:

The following is a list of maintained rejections:

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 24-31, 34-35, 38, 40-43 and 45-48 are rejected under 35 U.S.C. 102(b) as being anticipated by Price et al. (US 4,128,658).

The claimed invention is a method for preparing granules comprising wetting a mixture of active ingredient(s) and retarding agent(s) with an oily substance and granulating the wetted mixture.

Price teaches a method of producing oral sustained release tablets. "The active ingredient, anhydrous lactose and most of the Cutina HR (a hydrogenated castor oil) are intimately mixed and then the mixture is moistened by mixing with a 10% solution of the remainder of the Cutina HR ... the moistened mass is granulated through a 1.2 mm aperture sieve and dried at 50°C in a fluidised bed dryer. The granules are then passed through a 0.85 mm aperture sieve, blended with the magnesium stearate and compressed ... on a tableting machine with 12.5mm diameter punches" (Col. 29, Example c, lines 29-47). In another exemplified preparation (for an oral syrup), the drug is dissolved in water (Col. 29, line 56). Since the drug dissolves in water it is inherently hydrophilic.

Regarding instant claims 24 and 41, the limitations of a method for preparing granules comprising wetting a mixture of one or more active ingredients and one or more retarding agents with an oily substance are anticipated by the granulation method of an active ingredient mixed with anhydrous lactose and a hydrogenated castor oil taught by Price (Col. 29, Example c, lines 29-47). The retarding agent is the lipophilic hydrogenated castor oil. The wetting of the mixture is anticipated by the moistening by the hydrogenated castor oil. The granulation step is anticipated by the fluidized bed granulation step taught by Price. The limitation of compressing the granules so that tablets are prepared of instant claim 41 is anticipated by the compression of granules to form tablets as taught by Price.

Regarding instant claim 25, the limitation of the mixture further comprising excipients is anticipated by the excipient anhydrous lactose taught by Price (Col. 29, Example c, lines 29-47).

Regarding instant claim 26, the limitation of wetting the mixture by spraying is anticipated by the fluidized bed spray dryer taught by Price (Col. 29, Example c, lines 29-47).

Regarding instant claim 27, the limitation of wetting the mixture at room temperature is anticipated by method taught by Price (Col. 29, Example c, lines 29-47). Since Price does not disclose a specific temperature for the wetting or moistening step, one skilled in the art can readily envisage that the process is carried out at room temperature.

Regarding instant claim 28, the limitation of a hydrophilic active ingredient is anticipated by the active ingredient that dissolves in water, as taught by Price (Col. 29, line 56). Since the drug dissolves in water it is inherently hydrophilic.

Regarding instant claims 29-30, the limitation of the active ingredient content is anticipated by the 37.5% (1.5Kg/4Kg) of active ingredient as taught by Price (Col. 29, Example c, lines 29-47).

Regarding instant claim 31, the limitation of the lipophilic retarding agent is anticipated by the hydrogenated castor oil taught by Price (Col. 29, Example c, lines 29-47).

Regarding instant claims 34-35, the limitations of the oily substance and the percentage of the oily substance are anticipated by the 10% (0.4Kg/4Kg) of CUTINA HR® (hydrogenated castor oil) taught by Price (Col. 29, Example c, lines 29-47).

Regarding instant claim 38, the limitation of the fluidized bed granulator is anticipated by the fluidised bed dryer taught by Price (Col. 29, Example c, lines 29-47).

Regarding instant claim 40, the limitation of compressing the granules into tablets is anticipated by the tablets formed by compressing granules as taught by Price (Col. 29, Example c, lines 29-47).

Regarding instant claim 42, the limitation of mixing the granules with at least one excipient prior to compressing the granules is anticipated by mixing magnesium stearate with the granules before compressing into tablets as taught by Price (Col. 29, Example c, lines 29-47).

Regarding instant claim 43, the limitation of the excipient is anticipated by the lubricant magnesium stearate taught by Price (Col. 29, Example c, lines 29-47).

Regarding instant claims 45-48, the limitations of the granules and the tablet are anticipated by the granules and tablet prepared by the method taught by Price (Col. 29, Example c, lines 29-47).

Therefore, the limitations of claims 24-31, 34-35, 38, 40-43 and 45-48 are anticipated by the teachings of Price.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

10. Claims 32-33, 36-37, 39 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Price et al. (US 4,128,658) in view of Santus et al. (US 5,472,704).

The teaching of Price is stated above.

Price does not expressly teach the combination of the lipophilic retarding agent with a hydrogel matrix forming agent or a structural matrix forming agent.

Santus teaches bioadhesive granules with matrix units for the controlled release of furosemide (Col. 8, lines 63-64, Example 1). A hydrophobic matrix is obtained by granulation with melted excipients (Col. 8, lines 66-67). "50 parts of furosemide are mixed with 25 parts of hydrogenated castor oil and the resulting mixture is kneaded

using 25 parts of melted hydrogenated castor oil as a granulation fluid. The resulting mixture is granulated ... the granules are mixed with ... an acrylic copolymer and ... hydroxypropylmethylcellulose ... the mixture is then tableted in an eccentric press ... obtaining tablets with a diameter of 21mm. The tablets are then crumbled and sieved so as to obtain granules ..." (Col. 9, lines 1-12). A fluid bed system (WURBTER-GLATT®) is disclosed (Col. 8, lines 58-59). Excipients that are commonly known in the art are disclosed (Col. 7, lines 1-5).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the method of producing granules with an active ingredient and a lipophilic retarding agent, as suggested by Price, combine it with the method of producing granules of active ingredients with a lipophilic retarding agent in combination with acrylic copolymer and hydroxypropylmethylcellulose, as taught by Santus, and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because Santus teaches that cellulose derivatives such as hydroxypropylmethylcellulose (HPMC) are bioadhesive polymers. One of ordinary skill in the art would know that bioadhesive polymers are crucial for extended release formulations and would include it for extending the release of hydrophilic active ingredients.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of

ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Regarding instant claims 32-33, the limitations of the structural matrix forming agent and hydrogel matrix forming agent would have been obvious to one skilled in the art over the HPMC taught by Santus (Col. 9, lines 1-12). The limitation of the water soluble excipients would have been obvious over the anhydrous lactose taught by Price (Col. 29, Example c, lines 29-47).

Regarding instant claim 36, the percentage range of the oily substance would have been obvious over the 10% (0.4Kg/4Kg) of CUTINA HR® (hydrogenated castor oil) taught by Price (Col. 29, Example c, lines 29-47). One skilled in the art would modify the level of the oily substance during the process of routine experimentation in order to optimize the sustained or extended release attributes and the stability of the resultant granules.

Regarding instant claim 37, the limitation of the granules further comprising an outer phase of one or more retarding agents would have been obvious over the microunit coating taught by Santus. The method disclosed can coat individual microunits (Col. 8, lines 36-40).

Regarding instant claim 39, the limitation of the granule binder would have been obvious over the HPMC taught by Santus (Col. 9, lines 1-12).

Regarding instant claim 44, the limitation of the tablet further comprising a coating would have been obvious over the tablets taught by Price (Col. 29, Example c, lines 29-47) and because one skilled in the art would employ tablet coatings during the

process of routine optimization in order to enhance the stability and shelf-life of the tablet, to mask the off-notes, and to provide a layer of sustained release coating for extending the therapeutic effect of the chosen active ingredient.

Conclusion

11. No claims are allowed.
12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aradhana Sasan whose telephone number is (571) 272-9022. The examiner can normally be reached Monday to Thursday from 6:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached at 571-272-8373. The fax phone

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number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Aradhana Sasan/
Examiner, Art Unit 1615

/MP WOODWARD/
Supervisory Patent Examiner, Art Unit 1615